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Age-Associated Abnormalities of Water Homeostasis

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Introduction

Findley first proposed the presence of age-related dysfunction of the hypothalamic-neurohypophyseal-renal axis more than 60 years ago (1). His hypothesis was based on clinical observations that predated the first assays for arginine vasopressin (AVP). More sophisticated scientific methodologies have largely corroborated Findley's hypothesis of age-related dysfunction of the hypothalamic-neurohypophyseal-renal axis, and have further revealed the underlying physiologies that are part of the aging process. As a result, it is now clear that multiple abnormalities in water homeostasis occur quite commonly with aging, and that this group is uniquely susceptible to disorders of body volume and osmolality. This chapter will summarize the distinct points along the hypothalamic-neurohypophyseal-renal axis where these changes have been characterized, as well as the clinical significance of these changes with special attention to effects on cognition, gait instability, osteoporosis, fractures, and morbidity and mortality. This chapter represents a comprehensive update of our previously published review on this topic (2).

Physiological Overview of Disturbances of Water Metabolism

The ratio of solute content to body water determines the osmolality of body fluids, including plasma. As the most abundant extracellular electrolyte, the serum sodium concentration ($[Na^+]$) is the single most important determinant of plasma osmolality under normal circumstances. Although the regulation of water and sodium balance is closely interrelated, it is predominantly the homeostatic control of water, rather than of sodium, that determines serum $[Na^+]$, and therefore plasma osmolality. On the other hand, homeostatic controls of sodium metabolism and sodium-driven shifts in extracellular fluids more directly regulate the volume status of body fluid compartments rather than their osmolality. Isolated shifts in body water unaccompanied by shifts in body solute do not typically result in clinically significant changes in volume status. These isolated shifts in total body water, however, can result in dramatic changes in serum $[Na^+]$ and plasma osmolality (3). For example, in a 70

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kg adult, a 10% increase in total body water would cause a significant *decrease* in serum [Na^+] of approximately 14 mmol/L. Such a change could easily result in clinically significant hyponatremia and hypoosmolality. However, this same 10% gain of total body water would only cause an increase in intravascular volume of approximately 400 ml. Such a mild increase in circulating volume would not be expected to cause observable clinical findings. Similarly, the reverse situation of a 10% water loss would result in an *increase* in serum [Na^+] and clinically significant hyperosmolality, but without clinically significant hypovolemia (3). This is the case with uncompensated diabetes insipidus.

Physiologic processes that occur with aging are associated with changes in water metabolism and sodium balance, leading to alterations in plasma osmolality and body fluid compartment volumes. As a result of these changes, the elderly have increased frequency and severity of hypo- and hyperosmolality, manifested by hypo- and hypernatremia, as well as hypo-and hypervolemia. While the processes of water and sodium metabolism cannot be completely separated from each other, in this chapter we will focus mainly on the effects of aging on water balance and plasma osmolality.

Clinical Overview of Hyponatremia

Hyponatremia is the most common electrolyte disorder encountered in clinical practice (4). This hyponatremia becomes clinically significant when accompanied by plasma hypoosmolality. When hyponatremia is defined as a serum [Na^+] of <135 mmol/L, the inpatient incidence is reported to be between 15-22%. Studies that define hyponatremia as a serum [Na^+] <130 mmol/L demonstrate a lower, but still significant, incidence of 1-4% (5). Determination of a true incidence and prevalence of hyponatremia in the elderly is problematic. Several excellent observational studies examining this issue have been published, but the literature has lacked a uniform threshold for defining hyponatremia. The definition of the term “elderly” and criteria for age, stratification by serum [Na^+], medication use, and clinical setting vary widely between studies. Thus, direct comparisons among such clinical series are difficult. A recent review illustrates the disparate nature of the existing literature by pointing out that the incidence of hyponatremia in elderly populations has been reported to vary between 0.2-29.8%, depending on the criteria used to define both “hyponatremia” and “elderly” (6).

Miller et al. have published numerous observational studies on the elderly and hyponatremia. In a retrospective study of 405 ambulatory elderly patients with a mean age of 78 years, the incidence of serum [Na^+] <135 mmol/L was 11% over a 24-month observational period (7). These results are analogous to an earlier study by Caird et al. which reported that among healthy patients aged 65 or older living at home, the incidence of serum [Na^+] <137 mmol/L was 10.5% (8). Miller has also observed that the incidence of hyponatremia doubled to approximately 22% among elderly who reside in long-term institutional settings (9). He further noted that during a 1-year observational period, 53% of such institutional populations experienced one or more hyponatremic episodes (9). Another study by Anpalahan found similar results: 25% of patients aged 65 years and older who resided in an acute geriatric rehabilitation hospital had hyponatremia, defined as a serum [Na^+] <135 mmol/L (10). While true incidence of hyponatremia in the elderly is difficult to define given differing diagnostic criteria across studies, it is nonetheless clear that this problem cannot be considered to be an uncommon occurrence.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most common cause of hyponatremia in elderly populations. Cases of SIADH were first described by Bartter and Schwartz in 1957 (11) and the defining characteristics of the syndrome were summarized by the same authors 10 years later (12). The defining criteria presented in this

landmark publication remain valid and clinically relevant today. SIADH can be caused by many types of diseases and injuries common in the elderly, including central nervous system injury, pulmonary disease, malignancies, nausea, and pain. An idiopathic form of SIADH associated with aging has also been described. Several studies have demonstrated that SIADH accounts for approximately half (50-58.7%) of the hyponatremia observed in some elderly populations (7;10;13), and one-quarter to one-half (26-60%) of elderly patients with SIADH appear to have the idiopathic form of this disorder (7;10;13).

Clinical Implications of Hyponatremia

Hyponatremia is a strong independent predictor of mortality, reported to be as high as 60% in some series (14;15). Recent data has confirmed that hyponatremia in the elderly population is associated with multiple clinically significant outcomes in regards to neurocognitive effects and falls (16), osteoporosis (17), incidence of bone fractures (18), and hospital readmission and need for long-term care (19).

Terzian et al. studied the occurrence of admission hyponatremia and its association with in-hospital mortality in a geriatric patient cohort over age 65 admitted to a community teaching hospital (15). Serum [Na^+] <130 mmol/L within 24 hours of admission was the cutoff for inclusion. Of the 4,123 patients studied, 3.5% were hyponatremic. Higher prevalence rates were noted in women (4.6% vs 2.6%), patients who had not undergone operation (4.0% vs 2.4%), and those who had more than 3 diagnoses on admission (4.3 vs 1.9%). They noted that 16% of patients with admission hyponatremia died in the hospital as compared to 8% without hyponatremia. Relative risk of in-hospital mortality associated with admission hyponatremia was significantly increased at 2.0. This relative risk of mortality was higher for men than women, patients less than 75 years-old, and patients with malignancy or digestive disease. There was evidence of a linear association of in-hospital mortality with sodium level, with mortality increasing as sodium levels decreased. While this study could not establish the chronicity of hyponatremia at admission nor the underlying metabolic derangement, it suggested that the degree of hyponatremia may be an important indicator of poor prognosis for elderly hospitalized patients (15).

More recently, Wald et al. examined the entire spectrum of in-hospital hyponatremia in a group of adults presenting to a community academic hospital (19). This retrospect cohort study divided the patients into three categories: community-acquired hyponatremia (CAH; [Na^+] <138 mEq/L at the time of admission), hospital-aggravated hyponatremia (HAH; further decline in [Na^+] of at least 2 mEq/L in the first 48 hours of a CAH admission), and hospital-acquired hyponatremia (nadir serum [Na^+] < 138 mEq/L developing after hospital admission). The relationship between serum [Na^+] and predicted in-patient mortality is represented by a U-shaped curve (Figure 1), with [Na^+] of 140 mEq/L associated with the lowest risk of mortality. Increased mortality was significantly associated with [Na^+] <138 mEq/L and >142 mEq/L. CAH occurred in 37.9% of hospitalizations and was associated with an adjusted odds ratio of 1.52 for in-hospital mortality, 1.12 for discharge to a short- or long-term care facility, and a 14% increase in length of stay. HAH occurred in 38.2% of admissions and was associated with adjusted odds ratios of 1.66 for in-hospital mortality, 1.64 for discharge to a facility, and a 64% increase in length of stay. The strength of the associations increased along with severity of hyponatremia. Overall, this study highlighted the burden of hyponatremia on both patient outcomes and utilization of health care resources.

In addition to increases in inpatient mortality, recent studies have also demonstrated an increase in outpatient mortality associated with hyponatremia. Hoorn et al. examined the effect of hyponatremia on all-cause mortality within the framework of the Rotterdam Study,

an ongoing prospective longitudinal cohort study among outpatients older than 55 living in the Netherlands (20). A subset of 5,208 patients with baseline data on sodium concentration was included in their analysis. All-cause mortality was higher in subjects with hyponatremia than those without (51.6% vs 32.6%, p<.001). This increased risk remained after adjustment for age, sex, and BMI. After further adjustment for baseline comorbidities, the HR of all-cause mortality was 1.21 (95% CI 1.03-1.43, p=0.022) (20). This study suggests that hyponatremia should no longer be considered a benign condition in the outpatient elderly population.

Renneboog et al. conducted a case-control study to determine the functional significance of so-called “asymptomatic” mild chronic hyponatremia on cognitive impairment and falls (16). In this study, 122 Belgian patients with [Na^+] between 115-132, all judged to be asymptomatic at the time of emergency department (ED) presentation were compared with 244 age-, sex-, and disease-matched controls presenting during the same time period. All patients were assessed as to the primary reason for the ED visit. 21% of the hyponatremic patients presented because of a recent fall as compared to only 5% of controls, resulting in an adjusted odds ratio of 67 for hyponatremic patients presenting to an ED because of a fall. This data clearly demonstrated an increased incidence of falls in hyponatremic patients.

Renneboog et al. also evaluated the clinical implications of asymptomatic hyponatremia on attention deficits and gait instability (16). Sixteen patients with hyponatremia secondary to SIADH had comprehensive neurocognitive testing both before and after correction of their hyponatremia to normal ranges. When performing a series of attention tests, hyponatremic patients (mean [Na^+] =128±3) had prolonged median response latencies by 74 milliseconds as compared to the same patients after correction of their hyponatremia (mean [Na^+] =138±2); this effect proved to be greater than the 25 millisecond decrease in response latency induced in normal volunteers by acute alcohol ingestion (blood alcohol concentration =0.6±0.2 g/L). These impairments suggested a global decrease of attentional capabilities in hyponatremic patients that is greater than or equivalent to alcohol ingestion (16). A subset of 12 patients with [Na^+] in the range of 124-130 mEq/L was also tested for gait stability. The patients were asked to walk a tandem gait on a computerized platform that measured the center of gravity on the ball of their foot. Deviation from the straight line was measured as “Total Traveled Way (TTW). The hyponatremic patients wandered markedly off the tandem gait line in terms of their center of balance, but corrected significantly once their hyponatremia was corrected (Figure 2). As with the neurocognitive testing, this effect was greater than the gait instability induced in normal volunteers by acute alcohol ingestion. These results suggest that even mild degrees of hyponatremia can cause a significant gait instability that normalizes following correction of the hyponatremia, which may contribute to the increased incidence of falls in the elderly.

Four independent international studies have now demonstrated increased fracture rates in hyponatremic patients (21). Kengne et al. investigated the association between bone fracture, falls, and clinically asymptomatic hyponatremia in an ambulatory elderly population (18). 513 patients older than 65 who presented to the hospital with a bone fracture following an incidental fall were compared with 513 control subjects admitted during the same period but without a bone fracture. The prevalence of hyponatremia ([Na^+] <135 mEq/L) was 13.1% in patients with bone fractures compared to only 3.9% in the control patients, resulting in an adjusted odds ratio for bone fracture associated with hyponatremia of 4.16.

A retrospective study by Sandhu et al. showed similar findings (22). Investigators compared patients aged 65 and older presenting to the emergency department with fracture to those presenting for other reasons. Of 364 patients identified with fracture, 9.1% were

hyponatremic, accounting for a two-fold increase in fracture risk compared to the control group. Interestingly, 24.2% of the hyponatremic patients compared with 0% of controls were using selective serotonin reuptake inhibitors (SSRIs). SSRIs may cause hyponatremia, and both can cause sensorium and mobility deficits, contributing further to increased fracture risk (22).

Kinsella et al. also explored the association between hyponatremia and fracture and confirmed the findings of the two prior studies (23). They used a database which had been used previously to examine the association between self-reported fracture occurrence and chronic kidney disease. Of the 1400 individuals included in the database, 4.2% were hyponatremic with mean serum [Na^+] of 132.2 mmol/L. Compared with normonatremic patients, the hyponatremic patients were older and had a higher prevalence of osteoporosis. Hyponatremia was more common than normonatremia in the subset of patients experiencing fracture (8.7% vs 3.2%, $p<0.001$). Further regression models were tested indicating that the association between hyponatremia and fracture was independent of osteoporotic risk factors and osteoporosis treatment (23)

Finally, Hoorn et al. examined the relationship between mild hyponatremia and incidence of fracture within the framework of the prospective Rotterdam longitudinal aging study (20). Of the 5,208 patients mentioned previously, 399 patients (7.7%) were noted to be hyponatremic with mean serum [Na^+] of 133.4 mmol/L. Subjects with hyponatremia were older, had more recent falls, had increased prevalence of type 2 diabetes mellitus, and used more diuretics than the normonatremic controls. Hyponatremia was associated with increased risk of incident nonvertebral fractures (HR =1.39, 95% CI 1.11-1.73, $p=0.004$) after adjustment for age, sex, and BMI. Further adjustments for comorbidities and falls did not modify these results. Hyponatremic patients also demonstrated an increased risk of vertebral fractures at baseline but no association with bone mineral density. This increased risk of fracture was independent of falls, pointing toward a possible effect of hyponatremia on bone quality (20).

Verbalis et al. explored the effect of hyponatremia and bone quality and demonstrated a link between chronic hyponatremia and metabolic bone loss (17). In this study, Verbalis et al. used a rat model of SIADH to study the effects of hyponatremia on bone at the level of resorption and mineralization. Dual-energy X-ray absorptiometry (DXA) analysis of excised femurs established that hyponatremia for 3 months significantly reduced bone mineral density by approximately 30% compared with normonatremic control rats. Moreover, micro-computed tomography (uCT) and histomorphometric analyses indicated that hyponatremia markedly reduced both trabecular and cortical bone via increased bone resorption and bone formation. The most striking histologic finding was an increase in the number of osteoclast numbers per bone area and osteoclast surface per bone surface in the hyponatremic rats. This study demonstrated that chronic hyponatremia causes a significant reduction of bone mass at the cellular level. Follow-up studies confirmed that this process occurred in aging animals as well, though to somewhat lesser degrees than in the younger animals (Figure 3). The suggested reason for this phenomenon is that one-third of total-body sodium is stored in bone, and release of this sodium from bone during prolonged deprivation requires resorption of bone matrix.

To address the potential clinical relevance of this animal study, Verbalis et al. analyzed human data from the NHANES III survey, a cross-sectional survey that provided information on sodium concentrations and bone mineral density (BMD) of the hip in a nationally representative sample of US adults (17). The mean serum [Na^+] of the hyponatremic cohort of NHANES III was 133.0 mmol/L compared to 141.4 mmol/L in the normonatremic group. A statistically significant positive linear association between serum

[Na^+] and femoral neck BMD was observed in hyponatremic subjects. Among hyponatremic subjects, serum [Na^+] explained 14.7% of the variation in total hip BMD, and total hip BMD decreased by 0.037 g/cm^2 for every 1 mmol/L decrease in serum [Na^+]. The adjusted odds of osteoporosis at the femoral neck and total hip were significantly higher among participants with hyponatremia than normonatremia. The NHANES III data in humans support the experimental data in rodents and suggest direct clinical implications for these findings. Hyponatremia-induced bone resorption and osteoporosis are unique in that they represent attempts of the body to preserve sodium homeostasis at the expense of bone structural integrity. Finally, subsequent animal studies have implicated hyponatremia in the pathology of other organ systems (24), including the heart (Figure 4), skeletal muscle and gonads. This has led to the provocative hypothesis that hyponatremia may exacerbate multiple aspects of senescence, including osteoporosis, cardiomyopathy, sarcopenia, hypogonadism, and changes in body composition (24).

Clinical Overview of Hypernatremia

Hypernatremia necessarily reflects an increase in plasma osmolality. Cross-sectional studies of both hospitalized elderly patients and elderly residents of long-term care facilities show incidences of hypernatremia that vary between 0.3-8.9% (6;14). While hypernatremia is a common presenting diagnosis in the elderly, 60-80% of hypernatremia in elderly populations occurs after hospital admission (14). By the same token, up to 30% of elderly nursing home patients experience hypernatremia following hospital admission (25).

The clinical implications of hypernatremia in hospitalized elderly are significant. In a retrospective study, Snyder reviewed outcomes in 162 hypernatremic elderly patients, representing 1.1% of all elderly patients admitted for acute hospital care to a community teaching hospital (26). All patients were at least 60 years of age with a serum [Na^+] >148 mmol/L. Forty-three percent of these patients presented with hypernatremia at admission, and the remaining 57% developed hypernatremia after admission. Hypernatremia discovered at the time of admission was associated with greater age (mean age 81), female sex, and was more common in patients admitted from a nursing home. All-cause mortality in the hypernatremic elderly patients was 42%, which was 7 times greater than age-matched normonatremic patients. Furthermore, 38% of the hypernatremic patients who survived to discharge had a significantly decreased ability to provide self-care. Mortality among patients who presented with hypernatremia on admission was lower (29%) than mortality among patients who developed hypernatremia after admission (52%) despite higher peak serum [Na^+] in the former, compared with the latter group (26). The work by Wald et al. confirmed this association (Figure 1), noting a similar association between hypernatremia and increased predicted mortality risk in hospitalized patients with [Na^+] >142 mEq/L (19).

As hypernatremia develops, the normal physiologic response integrates renal water conservation through osmotically-stimulated secretion of AVP and accompanying potent stimulation of thirst (27). Although renal water conservation can forestall the development of severe hyperosmolality, only appropriate stimulation of thirst with subsequent increase in water ingestion can replace body fluid deficits and reverse existing hyperosmolality (3). This entire physiologic response is impaired with aging. Thus, the elderly have a greatly increased susceptibility to a variety of situations that can induce hypernatremia and hyperosmolality, with the attendant increases in morbidity and mortality that accompany the disorder (26;28).

Mechanisms Involved with Disturbances of Water Metabolism in the Elderly

Alterations in the regulation of water homeostasis in the elderly result from multiple consequences of aging: changes in body composition, alterations in renal function, and

changes in hypothalamic-pituitary regulation of thirst and AVP secretion (Table 1). The cumulative effect of these changes is a diminution of homeostatic reserve, as well as loss of appropriate corrective responses to environmental and metabolic stressors (29;30). Each of these potential mechanisms will be considered separately, and then combined into an integrated discussion of the etiologies of disorders of water metabolism in the elderly.

Changes in Body Composition with Aging

Aging typically leads to a 5-10% increase in total body fat, and a decrease in total body water of an equal magnitude. In an elderly 70-kg male, this can account for a reduction of total body water of as much as 7-8 liters compared with a young male of the same weight (29). With aging, plasma volume has also been shown to decrease by as much as 21% relative to body weight and surface area in older men when compared with younger controls (31). The consequence of these changes is that an equivalent acute loss, or gain, of body water will cause a greater degree of flux in osmolality in elderly compared to younger individuals. Thus, states of relatively mild dehydration or volume overload in the elderly are more likely to cause clinically significant shifts in concentration of body solutes, such as sodium. This was unequivocally demonstrated by Rolls et al. in a study that compared plasma osmolality in elderly and young subjects before and after equivalent degrees of fluid deprivation (30). Despite identical weight loss and similar changes in indices of plasma volume, the elderly clearly sustained a significantly greater increases in plasma osmolality than did the younger controls (Figure 5). A similar process likely accounts for the much higher prevalence of hyponatremia in the elderly as a result of retention of relatively smaller volumes of water.

Changes in Renal Function with Aging

Many aspects of renal function related to water homeostasis are under neurohormonal control via secretion of AVP from the posterior pituitary. However, intrinsic renal mechanisms that play a key role in the derangement of water balance in aging also exist. Typical age-associated changes in the kidney include loss of parenchymal mass, progressive glomerulosclerosis, tubulopathy, interstitial fibrosis, and the development of afferent-efferent arteriolar shunts (32). By age 80, the normal kidney loses up to 25% of its mass and develops a histopathological appearance similar to that seen in chronic tubulo-interstitial disease (28). Beck has described the resulting functional changes as an “inelasticity” in fluid homeostasis (28;29). Such defects may not be of immediate consequences during states of health, but in the elderly, especially under conditions of stress, disease, dehydration, or volume overload, such moderate impairments in normal renal physiology may cause significant imbalances in water and solute homeostasis (28). The clinical result is the development of depletional or dilutional states such as hyper- and hypoosmolality.

Age-Associated Changes in GFR—The Baltimore Longitudinal Study of Aging showed that up to 30% of healthy aged adults maintain a normal glomerular filtration rate (GFR). However, with few exceptions, in the remaining 70% of subjects, GFR was noted to decrease by approximately 1ml/min/1.73m^2/year after age 40. A further acceleration in the rate of decline after age 65 was also noted (28;33;34). Whether these changes are an inevitable consequence of aging, or are the result of subtle pathologic states remains uncertain. The consequences of such changes, however, are well established. Reductions in GFR increase proximal renal tubular fluid absorption, which leads to a decrease in tubular delivery of free water to the distal diluting segments of the nephron (14). The result is a loss of the dilutional capacity of the kidney, manifested by an impaired ability to excrete a free water load (25;30). Faull et al. studied free water excretion among elderly subjects (mean age 68) compared with young controls. That study showed that although the older group was able to achieve normal excretion following a standard water load of 20 ml/kg body weight, a

significant decrement in maximal free water clearance in the older group was present (35). Work by Clark et al. has suggested this may, in part, be caused by decreased distal renal tubular delivery of water due to reduced prostaglandin production in the elderly (36). Such impairment in the ability to excrete excess body water has direct implications in the susceptibility of the elderly to dilutional states that predispose to hypoosmolality and hyponatremia.

Loss of Urinary Concentrating Ability—Concomitant with the loss of diluting capacity, the aging kidney also loses the ability to maximally conserve body water during states of dehydration (37). In such a volume-depleted state, in the absence of fluid ingestion, maximal urinary concentration is the only means by which further losses of body water can be reduced. By age 80, maximal urinary concentration typically declines from a youthful peak of 1100-1200 mOsm/kg H_2O, to the range of 400-500 mOsm/kg H_2O (25). Phillips et al. established that following 24 hours of water deprivation, older subjects demonstrated significantly less urinary concentrating ability compared with younger controls despite higher levels of plasma osmolality. This effect was also noted to occur despite higher plasma AVP levels in the elderly, suggesting that the concentrating defect is predominantly due to intrinsic renal factors (38). The clinical implications of this age-acquired defect in the maintenance of normal plasma osmolality are clear. Loss of urinary concentrating ability contributes to the exacerbation of numerous conditions common in the elderly such as diarrhea, vomiting, decreased thirst, and poor oral intake, thus worsening the resulting dehydration, hyperosmolality and hypovolemia.

Changes in Centrally Mediated Control of Water Homeostasis with Aging

Central neuroendocrine control of AVP secretion and thirst are the major regulators of normal water balance in subjects with relatively normal renal function. Despite large variations in fluid intake, plasma osmolality is maintained within narrow limits via the secretion of AVP, the renal response to AVP secretion, and the appropriate control of thirst. Each of these processes is significantly affected by aging.

Regulation of AVP Secretion in Aging—AVP has a central role in the regulation of renal water excretion through its control of membrane insertion and abundance of the water channel aquaporin-2 (AQP2) in the distal nephron (39). These effects are mediated through AVP interaction with the type 2 vasopressin receptor (V2R) expressed in the renal collecting ducts. Increased membrane bound AQP2 increases water permeability of the collecting duct, and thereby induces a decrease in renal free water excretion, or antidiuresis. AVP is a nonapeptide synthesized by the cell bodies of the supraoptic and paraventricular nuclei of the hypothalamus. AVP is packaged in granules with its carrier protein neurophysin and transported down axons terminating in the posterior pituitary where it is stored and ultimately secreted in response to specific stimuli (27). The secretion of AVP is under exquisite, moment to moment control of osmoreceptors located in and around the organum vasculosum of the lamina terminalis and the anterior wall of the third ventricle. For any given individual, an osmotic threshold, or set point, for AVP release typically exists within a relatively narrow normal range. An increase in plasma osmolality as small as 1-2% is sufficient to cause an increase in plasma AVP concentration of 1 pg/mL. Such an increase is able to rapidly and significantly decrease free water excretion and reduce urine flow (27). Any increase in plasma osmolality above the set point, induces a linear increase in the secretion of AVP (14), with maximum antidiuresis occurring with plasma AVP concentrations above 5 pg/mL (27). This extraordinarily sensitive mechanism is able to maintain plasma osmolality within the range of 275 to 295 mOsm/kg H_2O. A secondary hemodynamic and volume dependent regulatory mechanism for AVP secretion also exists. This mechanism is controlled by baroreceptors located in the cardiac atria and large arteries.

In contrast to the exquisitely sensitive osmotic regulation of AVP secretion, the AVP response to a volume or hemodynamic stimulus does not occur until effective arterial volume is decreased by approximately 8-10% (14;27). The interaction of osmoreceptor and baroreceptor regulation of AVP secretion produces an integrated AVP secretory profile that is linear, but with a variable slope that is modulated by changes in volume and hemodynamic status (14).

Secretion and end organ effects of AVP are also affected by aging. A majority of studies have found that basal AVP levels in healthy elderly subjects are at least equal to, or more typically greater than those of young controls. However, a small number of studies have reported no differences in basal AVP levels in the elderly (40), and at least one study has suggested that basal AVP levels may be lower in older subjects (41). Regardless of basal AVP levels, most of the literature regarding water homeostasis has demonstrated that the elderly have a greater augmentation of AVP secretion per unit change in plasma osmolality than do younger subjects. This finding is consistent with an increase in osmoreceptor sensitivity in the elderly (41). Helderman et al. first made this observation over 35 years ago in studies of dehydrated elderly patients subjected to hypertonic saline infusions (Figure 6). Subsequent studies have repeatedly confirmed this observation (37;38;41;42). However, despite general agreement, a few notable exceptions exist. The early work of Phillips showed a three-fold increase in secretion of AVP per unit change in osmolality in the elderly (38), but later work by the same group, indicated that AVP secretion in response to osmolar stimulus is maintained rather than augmented (43;44). One isolated study demonstrating the absence of a correlation between AVP secretion and osmolality in the elderly also has been published (45). Nonetheless, preservation or more commonly augmentation of osmoreceptor sensitivity has been repeatedly confirmed in the elderly.

Several mechanistic explanations for observed age associated changes in AVP secretion have been proposed. Rowe et al. studied AVP secretory responses to orthostatic maneuvers in young and elderly subjects (46). That group found that 11 of 12 young subjects augmented AVP secretion in response to a position change from supine to erect. However, only 8 of 15, or just over half, of the elderly patients had a similar response (46). The study also demonstrated an appropriate increase in sympathetic nervous system discharge of norepinephrine in response to positional changes regardless of AVP secretory status. This suggests that aging may not affect AVP secretion through impairment of the baroreceptor afferent-efferent loop. Rather, the study concludes that aging may result in a loss of appropriate transmission of postural stimuli from the vasomotor centers of the brainstem where these stimuli are received, to the hypothalamus where secretion of AVP is controlled. Such a defect would thereby impair normal secretion of AVP in response to position changes. Based on these results, Rowe et al. have speculated that the increased AVP secretion in response to osmolar stimuli, which has been verified in the majority of studies performed in the elderly, may represent a compensatory response to the loss of normal baroreceptor mediated control of AVP secretion in response to hemodynamic changes (46).

While Rowe et al. suggest that the loss of baroreceptor influence on AVP secretion occurs due to loss of a neurologic pathway between the vasomotor center and the hypothalamus (46), Stachenfeld makes an argument for a role of atrial natriuretic peptide (ANP) as an important mediator of AVP secretion. This group employed studies of isosmotic central blood volume expansion during head out water immersion (HOI) and measured AVP responses in healthy elderly and young cohorts (42). They found that in addition to the loss of normal baroreceptor response to increases in central pressure, the elderly also demonstrated more exuberant secretion of ANP. They postulate that increased secretion of ANP may directly suppress AVP secretion during HOI (42). This hypothesis is consistent with earlier reports that exogenous ANP infusion suppresses osmotically stimulated AVP

release in both young and elderly subjects (47). However, other work has cast doubt on the relationship between ANP infusion and AVP secretion (48). Thus, the question of whether ANP exerts significant physiologic control over AVP secretion in the elderly remains unclear.

Regulation of AVP function in Aging—AVP V2 receptors, the site of AVP action in the kidney, are members of the seven-transmembrane domain G-protein coupled receptor family. Activation of the receptor by AVP induces production of the intracellular second messenger cyclic-AMP (cAMP) via activation of adenylyl cyclase. Through activation of the cAMP pathway, new aquaporin-2 (AQP2) water channels are synthesized and existing AQP2s are shuttled from intracellular storage vesicles and inserted into the apical plasma membrane of the renal collecting duct cells (49). Once inserted into the apical membrane, AQP2s form channels by which water molecules can be absorbed from the lumen of the collecting duct into the renal medullary interstitium driven by the medullary osmotic gradient. The resulting antidiuresis is capable of concentrating urine to an osmolality equivalent to that at the tip of inner renal medulla (27).

Since AVP levels are generally found to be elevated in the elderly, a pituitary secretory defect is unlikely to explain the decreased renal response to AVP noted in aging. A more likely explanation is a decrease in normal renal responsivity to AVP. Decreased V2R receptor expression and/or decreased second messenger response to AVP-V2R signaling would both result in loss of maximal urinary concentration. Both types of defects have been suggested in rat models of aging. A study in F344BN rats demonstrated an age-related impairment of renal concentrating ability after a moderate water restriction despite a normal AVP secretory response (39). This study found lower basal levels of AQP2 water channel expression in aging rats, and an inability of aging rats to normally upregulate AQP2 synthesis and mobilization despite appropriate AVP secretion. Other animal studies have suggested that decreased AVP-V2R signaling in the thick ascending limb and collecting ducts may also have deleterious effects on generation of the medullary concentrating gradient required for maximal urine concentration (50;51). Human studies have not been possible at this time; therefore the presence of such age-related changes in human kidneys remains speculative.

In addition to age-related changes in V2R expression and function, it has recently become clear that sex-related changes are clinically important as well. Studies in experimental animals have documented a 2.6-fold greater mRNA and 1.7-fold greater protein expression of the AVP V2R in female mice and rats compared to males (52). This is postulated to be a result of the location of the V2R on the X-chromosome, in a position that is predictive of incomplete inactivation of the V2R gene based on X-inactivation tests in heterozygous human fibroblasts (53). Clinical use of the AVP V2R agonist desmopressin for the treatment of enuresis in children and nocturia in adults has resulted in a small but significant incidence of hyponatremia, (54;55), which has occurred predominantly in elderly females. Recent clinical studies have demonstrated a greater sensitivity of females to smaller doses of desmopressin (56), consistent with the studies in experimental animals. The combined clinical and experimental studies therefore suggest that increased V_2R expression in females may cause greater sensitivity to the renal effects of exogenously administered AVP or desmopressin, and raises the possibility of similarly increased sensitivity to endogenously stimulated AVP thereby leading to hyponatremia from SIADH more frequently, particularly in elderly females who manifest other factors that limit water excretion.

Regulation of Thirst in Aging—Stimulation of thirst osmoreceptors produces signals that are conveyed to the higher cerebral cortex resulting in the perception of thirst and water-seeking behavior (3). The osmotic threshold for thirst is 5 to 10 mOsm/kg H_2O above that

for AVP release. This small difference in the set points regulating AVP secretion and manifestation of the thirst response has important physiologic consequences. Small osmolar excursions relative to an individual's osmotic set point induce changes only in AVP secretion and AVP-mediated changes in renal water excretion to maintain normal plasma osmolality. Only larger osmolar excursions are able to trigger the robust thirst response that either increases or decreases thirst in order to restore normal plasma osmolality. The important behavioral consequence of this mechanism is that the primary and earliest response to increased plasma osmolality involves an unconscious increase in AVP-mediated augmentation of renal concentration that occurs below the level of awareness. Only more pronounced increases in plasma osmolality are able to induce the potent and potentially disruptive behavioral response of water seeking.

Intrinsic defects in thirst clearly develop with aging. A study by Phillips et al. showed that older males deprived of hydration for 24 hours showed no subjective increase in thirst or mouth dryness and drank less water than young controls, despite significant increases in serum [Na^+] and plasma osmolality (38). Furthermore, in contrast to the young controls, when allowed free access to water, elderly subjects drank less and were unable to restore serum [Na^+] to pre-deprivation levels (Figure 7). These data suggest a blunted thirst response to osmotic changes in the elderly (57). One explanation for these findings has been offered by Mack et al. (58). This study showed that although a blunted thirst response was present in the elderly, the rate of fluid intake in healthy elderly and young controls was equivalent for equivalent degrees of thirst. Thus, elderly subjects appeared to have a higher osmolar set point for thirst. This results in a decrease in the degree of perceived thirst for any given level of plasma osmolality, leading to a net decrease in the amount of fluid ingested due to a decrease in the thirst response (58). In contrast, other studies of thirst in the elderly that utilized hypertonic saline infusions and HOI have suggested that the response of thirst to an osmotic stimulus unaccompanied by a change in plasma volume is not appreciably affected by normal aging (41;42). Instead, these studies demonstrated a diminution of baroreceptor-mediated regulation of thirst in response to changes in plasma volume (59). Studies employing HOI have supported the concept that control of thirst by volume shifts may actually take priority and override contradictory osmotic stimuli, at least in young subjects (60). Using this same method, Stachenfeld has demonstrated that in carefully selected healthy dehydrated participants, HOI caused a greater suppression of thirst and drinking response in the young compared to the elderly subjects (42). This study found that although net thirst was not different between the elderly and the young, this was due to relatively greater baroreceptor-mediated suppression of more exuberant thirst in the young compared to the elderly subjects. These combined data, therefore, provide further evidence of an intrinsic defect in thirst with normal aging.

The subjective sensation of thirst requires unimpaired transmission of efferent signals from hypothalamic osmoreceptors to the cerebral cortex where thirst is perceived. Although the neural pathways that conduct these signals are not well characterized, it is likely that one of the major factors responsible for age-related changes in thirst is impairment of these poorly defined efferent pathways (43). Subtle and cumulative brain injury due to age-associated illness rather than aging, *per se*, may play an active role in such a process. It has been suggested that elderly patients who had many types of mild chronic illness may not have been adequately excluded from study populations previously described as “healthy”. How the possible inclusion of such patients may have colored early studies of aging is difficult to assess (40;41). Nonetheless, well-controlled studies on highly selected groups of healthy elderly subjects appear to corroborate the early findings of the presence of intrinsic defects in thirst with normal aging. Most studies confirm that aging is accompanied by decreased thirst. However, the relationships among osmolar changes, volume status, and other stimuli, and how these interact to mediate thirst with aging remains incompletely understood. Thirst

is a complex response to multiple and frequently interrelated physiologic stimuli. The literature provides observations of numerous stimulus response mechanisms involved in the generation and perception of thirst, and changes associated with aging. The exact mechanisms by which these changes occur, and whether they are an unavoidable consequence of normal aging, remain to be ascertained.

Integration of Changes in AVP Secretion, Thirst and Kidney Function with Aging

Beck's conceptualization of “homeostatic inelasticity” aptly describes the consequences of the spectrum of physiological changes that occur with aging (28). Aging causes distinct changes that impact normal water homeostasis at several discreet locations along the neuro-renal axis responsible for maintaining normal water balance. As a result of these changes, the elderly experience a loss of homeostatic reserve to compensate for both decreases and increases in body fluids and osmolality. The net effect is increased susceptibility to pathologic and iatrogenic causes of disturbed water homeostasis, both a decreased ability to conserve and obtain fluids, leading to dehydration and hyperosmolality, and a decreased ability to excrete fluids, leading to overhydration and hypoosmolality.

The *primary* threat to dehydration and hyperosmolality appears to be a reduced sensation of thirst leading to a compromised drinking response to thirst in the elderly. It is likely, as Phillips et al. have suggested, that part of this defect is through loss of normal neural pathways that convey sensory input to the higher cortical centers where thirst is perceived, and from which the thirst response emanates (44). A clear age-related deficit in the thirst response appears to arise from decreased sensitivity to osmolar stimulation. The early work of Phillips et al. demonstrated the presence of such a defect (57), and subsequent studies by Mack et al. suggest that this defect is due to a higher osmotic set point leading to a blunted thirst response in the elderly (58). Most importantly, the loss of an appropriate thirst response compromises the critical compensatory mechanisms responsible for the drive to replace lost body fluid, and the only true physiological means of correcting a hyperosmolar state.

Impaired GFR and resultant loss of maximal urinary concentrating ability also contribute to the threat of dehydration and hyperosmolality with aging. Decreased renal function is a common, if not certain, consequence of aging (34;61). While it appears that the development of such a deficit is not inevitable, how to discern which elderly are most likely to suffer such a loss is not easily determined. Since the majority of otherwise “normal” elderly patients manifest such a decrement in renal function, the argument regarding whether such a change is inevitable or not may be overly academic. It may, on the other hand, be appropriate to assume that such a defect is probable, though some elderly who age more “successfully” than others may maintain reasonably normal renal function. Whenever the onset and progression of this process, consequence is clear: decreased GFR causes an inability to maximally conserve free water and favors development of inappropriate body water deficits. In addition to decrements in GFR, animal studies have unequivocally indicated an accompanying age-acquired end organ insensitivity to the effects of AVP (62), which would have the effect of magnifying renal water losses with aging. These combined effects likely initiate the pathophysiological pathway leading to mild hyperosmolality in the elderly, which is then exacerbated by impaired thirst and drinking in response to the hyperosmolality leading to more clinically pathological degrees of hypernatremia and hyperosmolality.

The *primary* threat to overhydration and hypoosmolality appears to be a decrement in maximal water excretion that paradoxically also occurs in the elderly (35;36). Such a defect would have significant clinical consequences in situations of inadvertent or forced

overhydration. The elderly are at a higher risk of developing diseases such as congestive heart failure that are associated with volume overload. So too, are the elderly at risk for inadvertent iatrogenic overhydration from intravenous and enteral hydration therapy. Any inability to appropriately excrete an excessive fluid load would predispose elderly individuals to the development of overhydration and hypoosmolality. The secretion and end organ effects of AVP account for two of the most interesting, and perhaps least well understood aspects of water regulation in the elderly. Although a few exceptions exist, most agree that basal AVP secretion is at least maintained, and more likely increased, with normal aging (27). Further, the AVP secretory response, i.e., the osmoreceptor sensitivity to osmolar stimuli, is also increased in normal aging (41). Thus, AVP secretion represents one of the few endocrine responses that increases rather than decreases with age. Although renal responsiveness to AVP may be reduced with aging, it is certainly not entirely eliminated. This may underlie the increased incidence of idiopathic SIADH that occurs in the elderly that often cannot be explained by identifiable pathologies (7).

We hypothesize that enhanced secretion of AVP in the elderly and inability to appropriately suppress AVP secretion during fluid intake (44), combined with an intrinsic inability to maximally excrete free water (35;36), increase the likelihood that SIADH will occur in this group of patients. We believe these factors may explain the unusually high incidence of idiopathic SIADH noted in elderly populations. Direct experimental proof of this hypothesis is still required. Nonetheless, the preponderance of existing experimental data suggests that this assumption is well founded.

Although excessive fluid intake is likely not the major cause of hypoosmolality in most elderly patients, nonetheless it may also contribute to the threat of overhydration and hypoosmolality with aging. Stachenfeld's studies have clearly demonstrated that plasma volume expansion in elderly subjects does not generate the normal suppression of thirst found in the young (42). Thus, absent suppression of thirst would be likely to aggravate the effects of excessive renal water retention in elderly patients leading to more pathological degrees of hyponatremia and hypoosmolality in the elderly

In conclusion, much has been learned in six decades since Findley's original reflections about the effects of aging on water homeostasis. Since then, clearly demonstrated deficits in renal function, thirst and responses to osmotic and volume stimulation have been repeatedly demonstrated in this population. Although much is already known about the renal actions of AVP at the V2 receptor, this area remains an active area of study with regard to age-induced changes in renal concentrating ability, including how these effects interact with sex-related differences in V2R expression and function. The lessons learned over the past six decades of research serve to emphasize the fragile nature of water balance that is characteristic of aging. The elderly are at increased risk for disturbances of water homeostasis due to both intrinsic disease and iatrogenic causes. Recent studies have now shown that these disturbances have real-life clinical implications in terms of neurocognitive effects, falls, osteoporosis, bone fractures, hospital readmission and need for long-term care, and morbidity and mortality. It is therefore incumbent upon all those who care for the elderly to realize the more limited nature of the compensatory and regulatory mechanisms that maintain normal fluid homeostasis in elderly patients, and to incorporate this understanding into the diagnosis and clinical interventions that must be made to provide optimal care for this uniquely susceptible group of patients.

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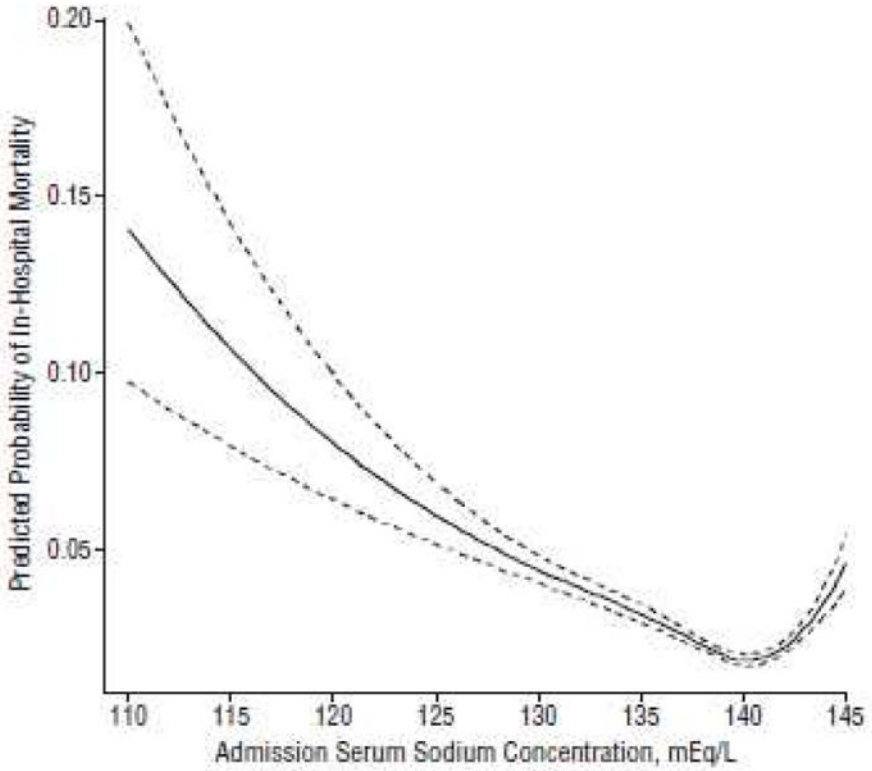

Figure 1.

Restrictive cubic spline depicting the unadjusted relationship between hospital admission serum sodium concentrations and predicted probability of in-hospital mortality. Dashed lines represent the 95% confidence interval. (*From* Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. Arch Intern Med 2010; 170(3):294-302)

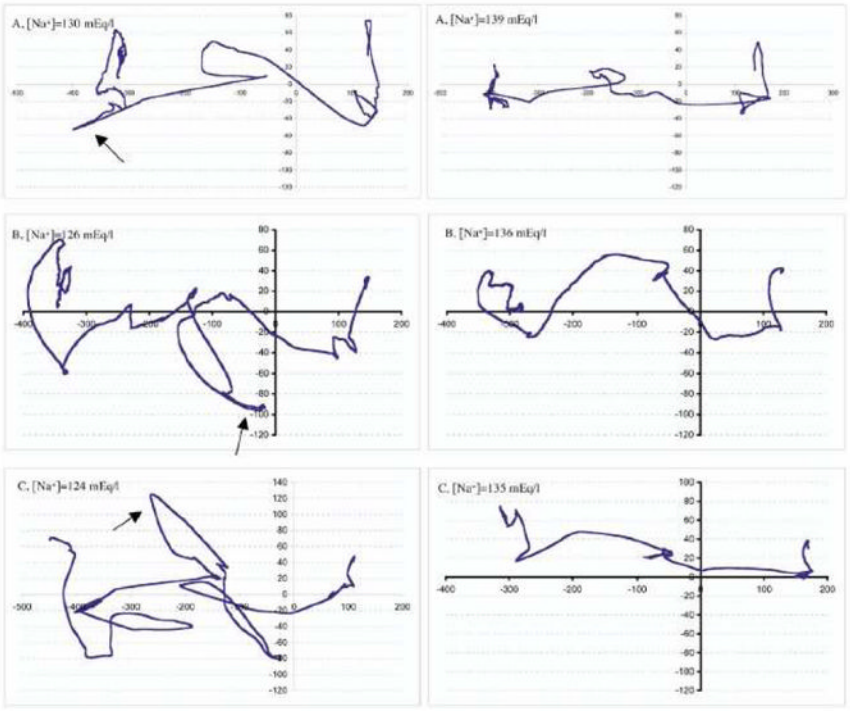

Figure 2.

"Total traveled way" (TTW) measured by the center of pressure during a dynamic walking test consisting of 3 stereotyped steps "in tandem," eyes open, in 3 patients (A, B, C) with mild asymptomatic hyponatremia before (left) and after correction (right). Patients are walking from right to left. Markedly irregular paths of the center of pressure were observed in the hyponatremia condition (arrows). (*From* Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med 2006; 119(1):71)

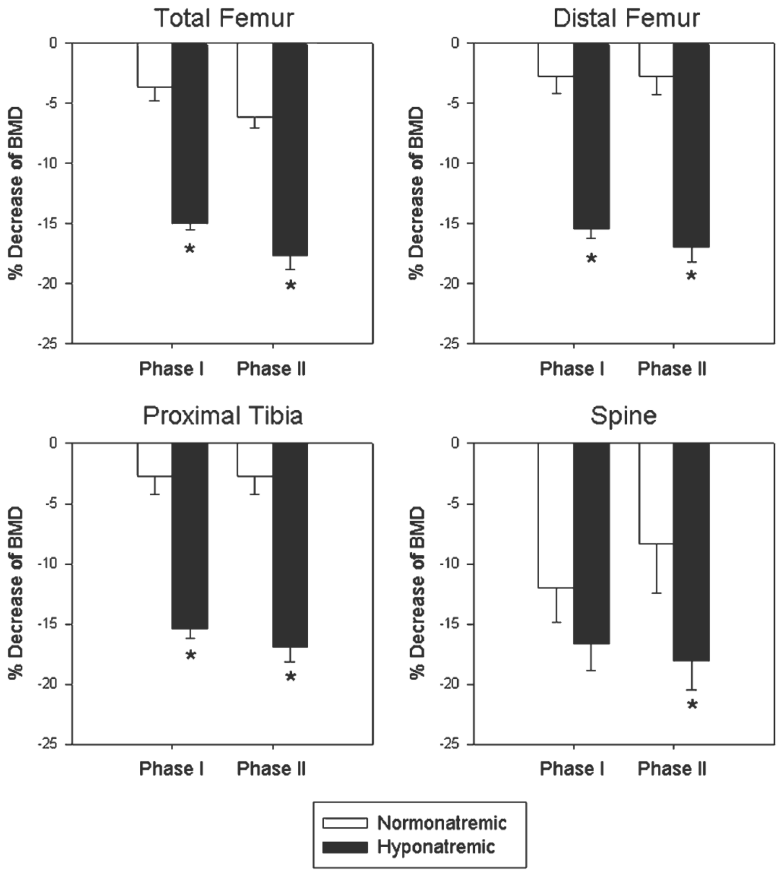

Figure 3.

Changes of bone mineral density (BMD) at multiple sites at the end of phase I (10 weeks) and phase II (18 weeks) in normonatremic (open bars) and hyponatremic (black bars) aged F344BN rats (22 months old at the start of the study). The BMD decreases from baseline were significantly greater in the hyponatremic rats than in the normonatremic rats ($p<0.001$). During phase II, hyponatremic rats received high dose vitamin D supplement that mitigated further declines of BMD. Asterisks indicate statistically significant differences from the normonatremic controls. (*From* Barsony J, Manigrasso MB, Xu Q, Tam H, Verbalis JG. Chronic hyponatremia exacerbates multiple manifestations of senescence in male rats. Age, 2012, Jan 5. [Epub ahead of print])

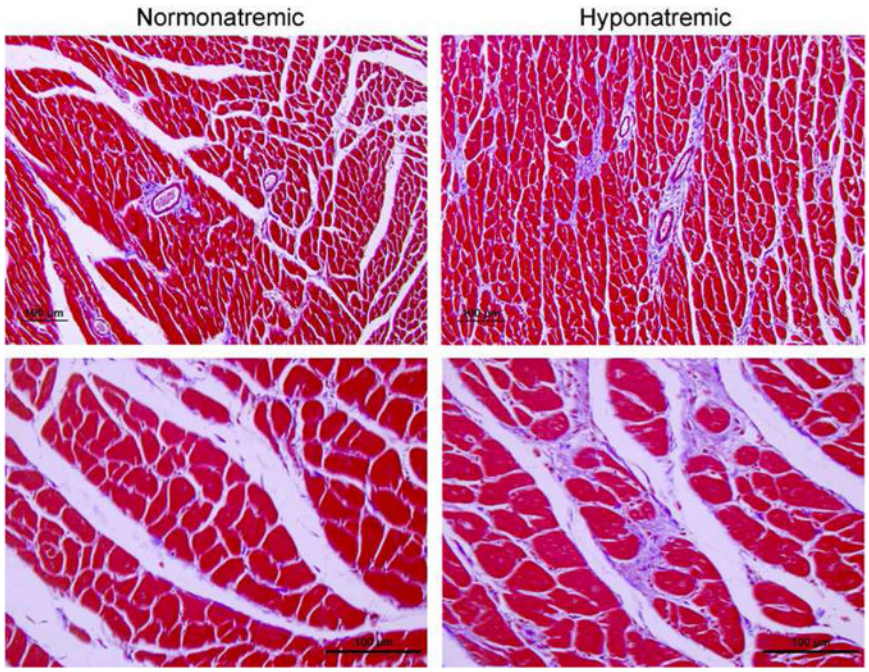

Figure 4.

Histology of hearts from normonatremic and chronically hyponatremic aged F344BN rats. Representative low-power (20× objective; upper panels) and high power (40× objective; lower panels) microscopic images of 5-micron sections from the hearts stained with Masson's trichrome protocol that marks collagen fibers with blue color. Note increased interstitial and perivascular collagen deposits in micrographs of the left ventricle from hyponatremic rats (right panels) compared to micrographs from normonatremic rats (left panels). (*From* Barsony J, Manigrasso MB, Xu Q, Tam H, Verbalis JG. Chronic hyponatremia exacerbates multiple manifestations of senescence in male rats. Age, 2012, Jan 5. [Epub ahead of print])

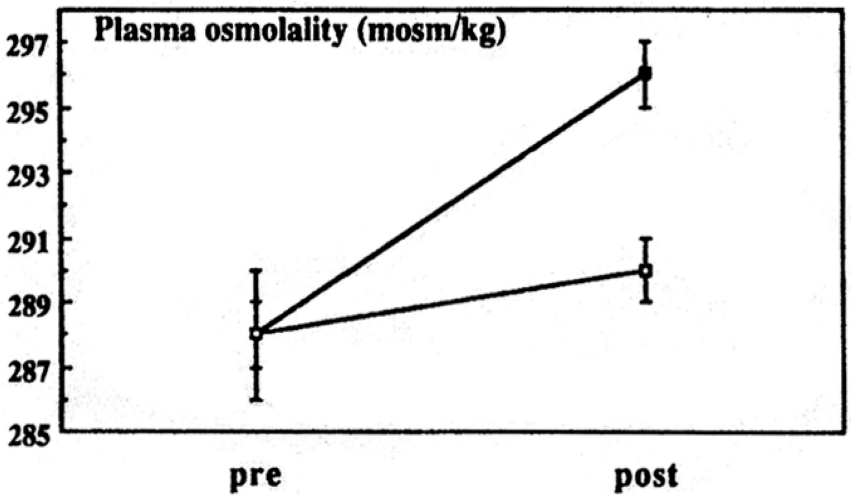

Figure 5.

Mean changes, pre and post fluid deprivation in young (open boxes) and elderly (closed boxes) subjects after equivalent degrees of induced weight loss. (*From* Rolls BJ, Phillips PA. Aging and Disturbances of Thirst and Fluid Balance. Nutrition Reviews 48:137. 1990)

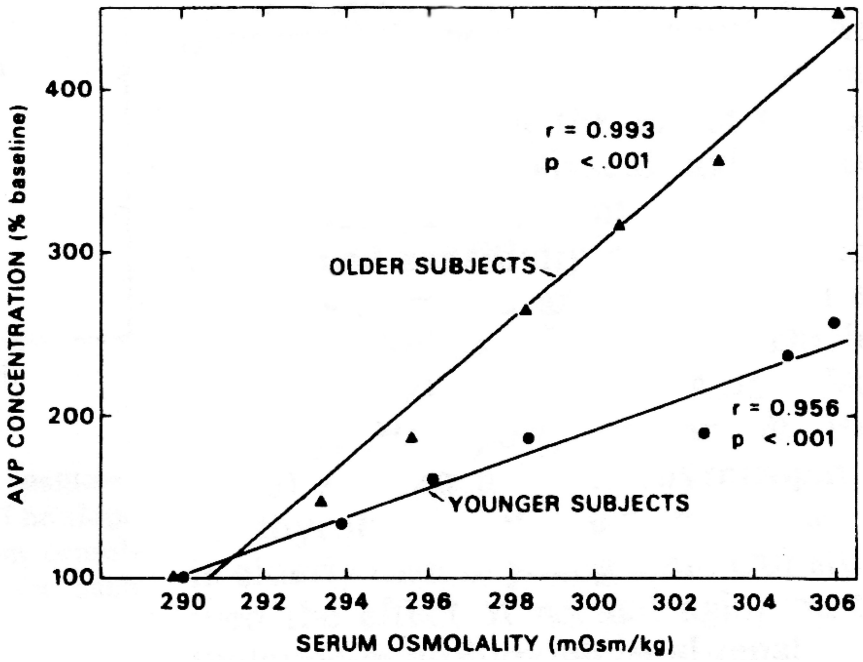

Figure 6.

Correlation between serum osmolality and AVP concentration in 8 young and 8 older subjects during a 2-hour 3% saline infusion following mild dehydration. The older subjects had significantly higher plasma levels of AVP per unit increase in plasma osmolality, strongly suggesting an enhanced osmotically-stimulated secretion. (*From* Helderman JH. The response of arginine vasopressin to intravenous ethanol and hypertonic saline in man: The impact of aging. J Gerontol 1978;33(1):39-47)

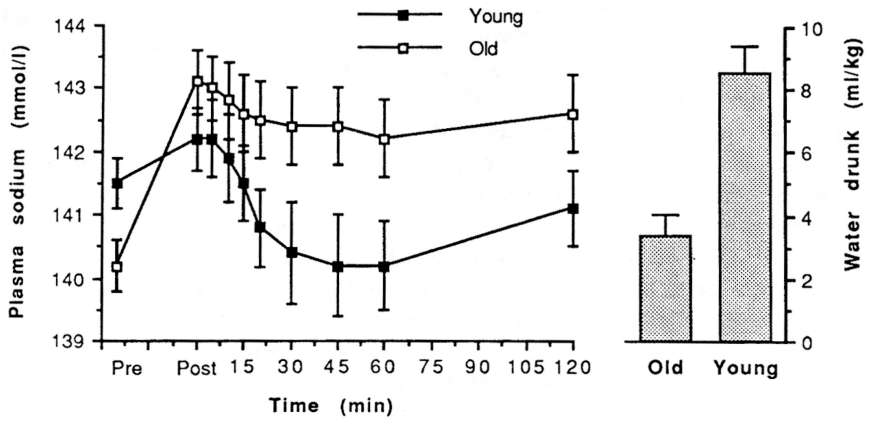

Figure 7.

Plasma sodium concentration and total water intake in healthy elderly and young subjects following 24 hours of dehydration. Baseline sodium concentration before dehydration (pre) and after dehydration (post) are shown. Free access to water was allowed for 60 minutes following dehydration starting at time=0 minutes. Cumulative water intake during the free drinking period by young and old subjects is depicted in the bar graph. Despite a greater initial increase in serum [Na^+], elderly subjects drank significantly less water, resulting in lesser correction of the elevated serum [Na^+]. (*From* Phillips PA, Johnston CI, Gray L. Disturbed fluid and electrolyte homeostasis following dehydration in elderly people. Age and Aging 1993;22:26-33)

Table 1

Multiple factors that impair maintenance of normal body fluid homeostasis with aging.

Altered body composition:
Reduced plasma volume
Increased osmolal flux
Kidney effects:
Impaired free water excretion
Decreased urine concentrating ability
Brain effects:
Decreased thirst perception
Increased AVP secretion